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PREPARATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF METFORMIN HYDROCHLORIDE TABLETS

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ABSTRACT

Metformin HCl sustained release matrix tablets were prepared by direct compression. All the tablets were prepared under identical conditions to minimize the processing variables. Tablet formulations were further evaluated for physical parameters. It was revealed that all the tablet formulations were found to be stable and meeting I.P specified limits for weight uniformity, friability, drug content. Drug content estimated for all the tablet formulations were highly uniform with less than 2.5% variation. Drug content was also the same in case of matrix tablets containing polymers. The matrix tablet formulations prepared with drug and polymer of guar gum in F5 could be suitable for extending the drug release more than 12 hrs.

Key words: Metformin HCl, sustained release matrix.

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INTRODUCTION

Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. The advantage of administering a single dose of a drug that is released over an extended period of time is to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use. The first sustained release tablets were made by Howard Press in New Jersey in the early 1950's. The first tablets released under his process Patent were called 'Nitroglyn' and made under license by Key Corp. in Florida. Sustained release, prolonged release, modified release, extended release or depot Formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulations. If the active compound has a long half-life, it is sustained on its own, If the pharmacological activity of the active is not directly related to its blood levels, If the absorption of the drug involves an active

transport and if the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose. The above factors need serious review prior to design. Some drugs are inherently long lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up doses and noncompliance with the regimen. When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose (Fig.1). However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of sub therapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient. Extended-release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended-release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period (Fig.2). The sustained plasma drug levels provided by extended-release products often times eliminate the need for night dosing (1-3).

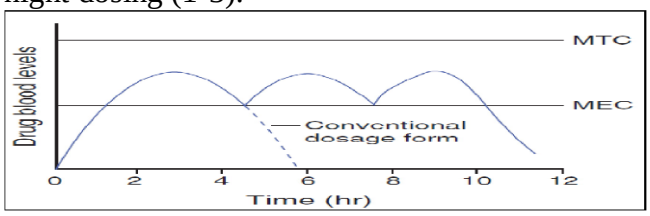

Fig-1 Hypothetical drug blood level–time curves for a conventional solid dosage form and a multiple action product.

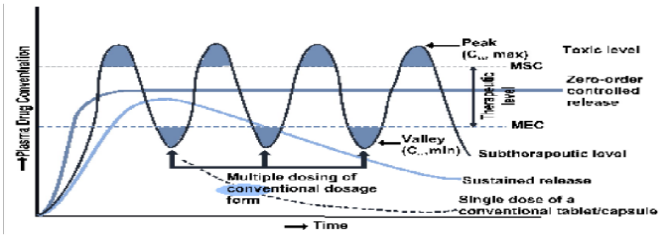

Fig-2 Hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and sustained delivery formulations.

The aim of the present study is to formulate and evaluate sustained release matrix tablets of Metformin Hydrochloride**.** Metformin Hydrochloride is a biguanide that has been used for the treatment of Type 2 diabetes. To Formulate and Evaluate Sustain release matrix tablets of Metformin Hydrochloride by using various rate controlling polymers. To study the effect of nature (hydrophilic, hydrophobic and plastic) of the polymer and drug: polymer ratios on the rate of drug release. To study the effect of different concentrations of synthetic and natural polymers on drug release rate. Sustained release drug delivery systems have received much attention in the past two decades with numerous technologically sophisticated products on the market place. Such advancements have come about by convergence of many factors, including the discovery of novel polymers, formulation optimization, better understanding of physiological and pathological constraints, prohibitive cost of developing new drug entities and the introduction of biotechnology and biopharmaceutical principles in drug product design. The major benefits of these products lie in the optimization of drug input rate into the systemic circulation in order to achieve an appropriate pharmacodynamic response.

MATERIALS AND METHODS (4-8)

Preparation of Metformin Hcl Matrix Tablets

All the matrix tablets, each containing 500 mg ofMetformin HCl, were prepared by direct compression method. Accurately weighed amounts of drug, polymer, and diluent were mixed geometrically in a mortar. This mixture was passed through No.40 sieve and thoroughly mixed in a polythene bag for 15 minutes. The powder blend was then lubricated with magnesium stearate and for 2 minutes and compressed into tablets on a 16-station rotary tableting machine.

The drug polymer ratio was developed to adjust drug release as per theoretical release profile and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets was 1000mg with different drug polymer percentages. The various polymers used were HPMC K100M, Guargum, Eudragit RL100 and xanthan gum, fillers like MCC, lubricants like magnesium stearate were used for the preparation of matrix tablets.

***In vitro* Studies**

The formulations which showed good *in vitro*

performance were subjected to accelerated stability studies. These studies were carried out by investigating the effect of temperature on the physical properties of tablets and chemical stability of tablets containing drug. The tablet formulations such as were subjected to accelerated stability studies. The above said formulations were kept in petridishes after preparation and stored in thermostated oven at a temperature and relative humidity of 25 ± 20C, 60 ± 5% RH for 6 months and 40 ± 20C, 75 ± 5% RH for 3 months. Then the samples of each type of formulations were evaluated for the earlier mentioned physical parameters.

The tablets were evaluated for physical parameters and the drug was analyzed for drug content uniformity by a known spectrophotometric method as described earlier. Further these were subjected to drug release studies as stated earlier.

RESULTS AND DISCUSSION

Estimation of Metformin HCl

The spectrophotometric method used for the estimation of Metformin Hydrochloride in the dissolution medium was found to be linear and reproducible. This method obeyed beer's law in the concentration range of 2 to 10 µg/ml. Reproducibility of the method was tested by analyzing 6 separately weighed samples of Metformin Hydrochloride. Thus, the method was found to be suitable for the estimation of Metformin hydrochloride in dissolution media. The values were given in Table-1 and calibration curve was shown in Figure- 3.

Table-1 Standard Graph of Metformin HCl in 0.1 N HCLbuffer at 233 nm

S.No.	Concentration	Absorbance
	0	0
	2	0.0422
	4	0.0813
	6	0.1238
	8	0.1561
	10	0.1971

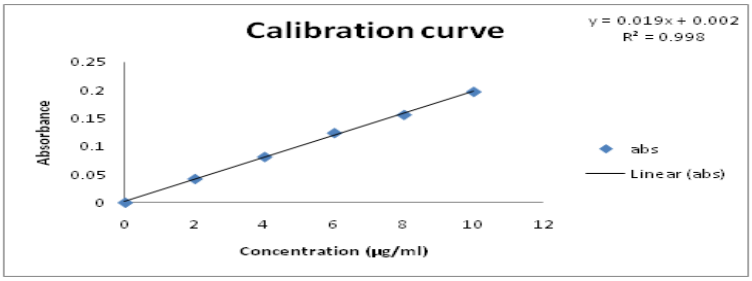

Fig-3 Standard calibration curve for Metformin HCl in 0.1 N HCl

Preparation of Metformin HCl Matrix Tablets:

Metformin HCl matrix tablets were prepared by Direct compression method.Accurately weighed amounts of drug, polymer, and diluent were mixed geometrically in a mortar (Table-2). This mixture was passed through No.40 sieve and thoroughly mixed in a polythene bag for 15 minutes. The powder blend was then lubricated with magnesium stearate for 2 minutes and compressed into tablets on a 16-station rotary tableting machine.The prepared Tablets were evaluated for flow properties such as angle of repose and compressibility index. To minimize the processing variables, all batches of tablets were compressed under identical conditions.

Evaluation of Physical Parameters of Metformin HCl Matrix Tablets:

Direct compression method was found to be suitable for preparing matrix tablet formulations. All batches of tablets were compressed under identical conditions to minimize the processing variables. Then the compressed matrix tablets were further evaluated for physical parameters such as weight uniformity, hardness, friability and drug content.

These studies revealed that all the tablet formulations were found to be stable and meeting I.P specified limits for weight uniformity, friability and drug content.
The hardness of all the tablet formulations was in the range of 4.0 to 4.8 kg/cm2. Weight uniformity of all the tablet formulations were in the range of 1000 ± 3 mg/tablet. Friability loss of all the tablet formulations was negligible and was in the range of 0.1 to 0.2%. Drug content estimated for all the tablet formulations was highly uniform with less than 2.5% variation.

Table-2

Formulation Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Metformin HCl	500	500	500	500	500	500	500	500	500	500	500	500
HPMC	200	250	300	---	---	---	---	---	---	---	---	---
Guargum	---	---	---	200	250	300	---	---	---	---	---	---
Xanthan gum	---	----	----	----	---	---	200	250	300	---	---	----
Eudragit	---	---	---	---	---	---	---	---	---	200	250	300
MCC	280	230	180	280	230	180	280	230	180	280	230	180
Magnesium stearate	20	20	20	20	20	20	20	20	20	20	20	20
Total amt (mg/tab)	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000

***In vitro* Dissolution Studies**
Dissolution studies were performed on all the tablet formulations by using U.S.P paddle method (apparatus II). Dissolution Profiles of Metformin Hcl matrix tablets were given in in Figures 4-7. The drug release from the matrix tablet formulations were extended up to 12hrs in majority of the formulations. Formulations F1, F2 and F3 failed to release the drug up to 12hrs which were prepared by using different concentrations of HPMC K100M as rate retarding polymer and without electrolytes. The formulation F5 containing drug and Guar gum with increasing concentration retarded the drug release up to 12hrs. It was found that increase in the concentration of polymer resulted in delay in the drug release. The drug release in F1,F2,F3 formulation containing drug and HPMC K100M as polymer was extended up to 6,8,8 hrs respectively. The drug release in F4,F5,F6 formulation containing drug and Guar gum as polymer was extended up to 8,12,12 hrs respectively. The drug release in F7,F8,F9 formulation containing drug and Xanthan gum as polymer was extended up to 4,6,8 hrs respectively. The drug release in F10,F11,F12 formulation containing drug and Eudragit RL100 was extended up to 6,8,8 hrsrespectiely. It was observed that the concentration of Guar gum in the matrix tablet formulations increased, the retardation in drug release. Guar gum is hydrophilic in nature and hence the formulations containing the polymer showed more swelling characteristics and drug release was extended up to 12hrs. Formulations prepared by employing electrolytes were found to extend the drug release more than 12hrs. The drug release from the matrix tablet formulations was extended up to 12hrs in the formulations F5 containing Guar gum as rate controlling polymer.

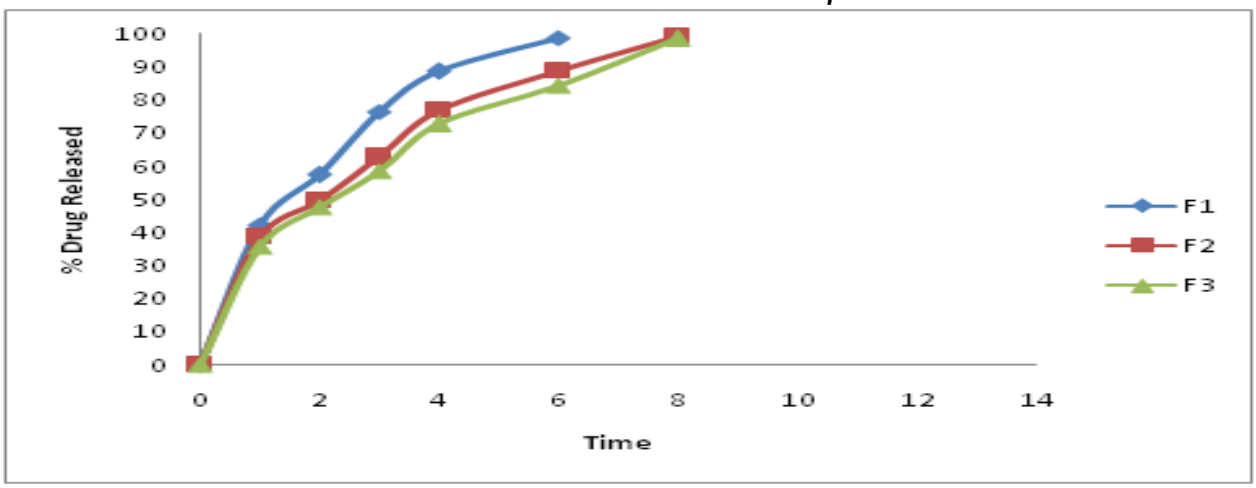

Fig-4 Drug Release Profiles of Metformin HCl Matrix Tablets

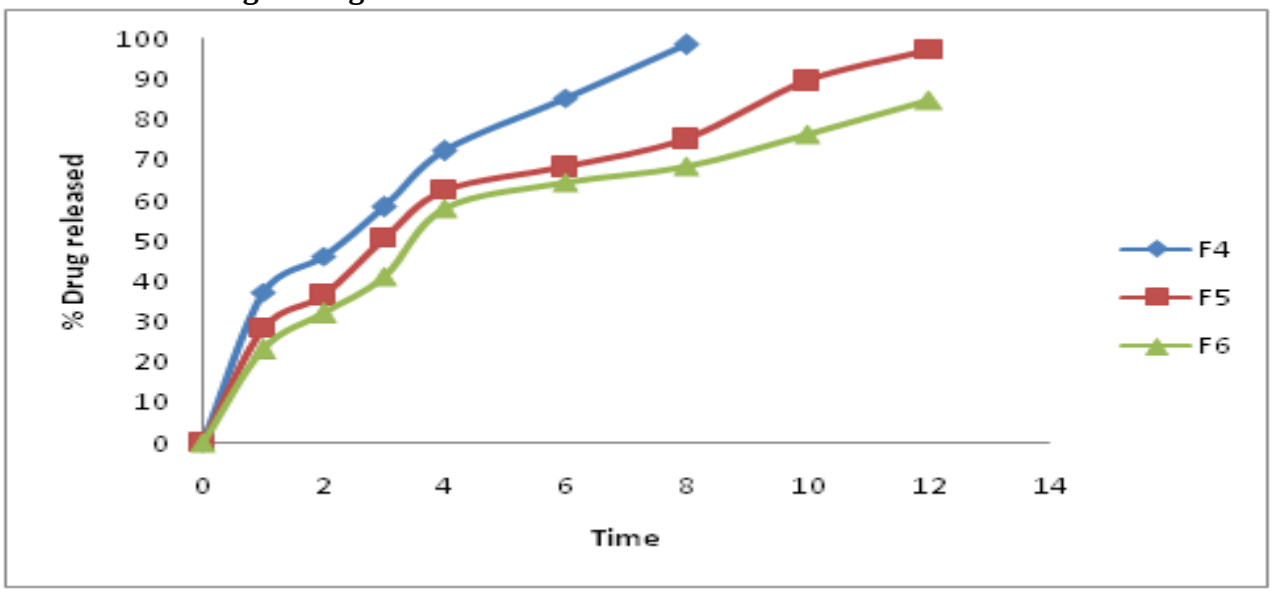

Fig-5 Drug Release Profiles of Metformin HCl Matrix Tablets

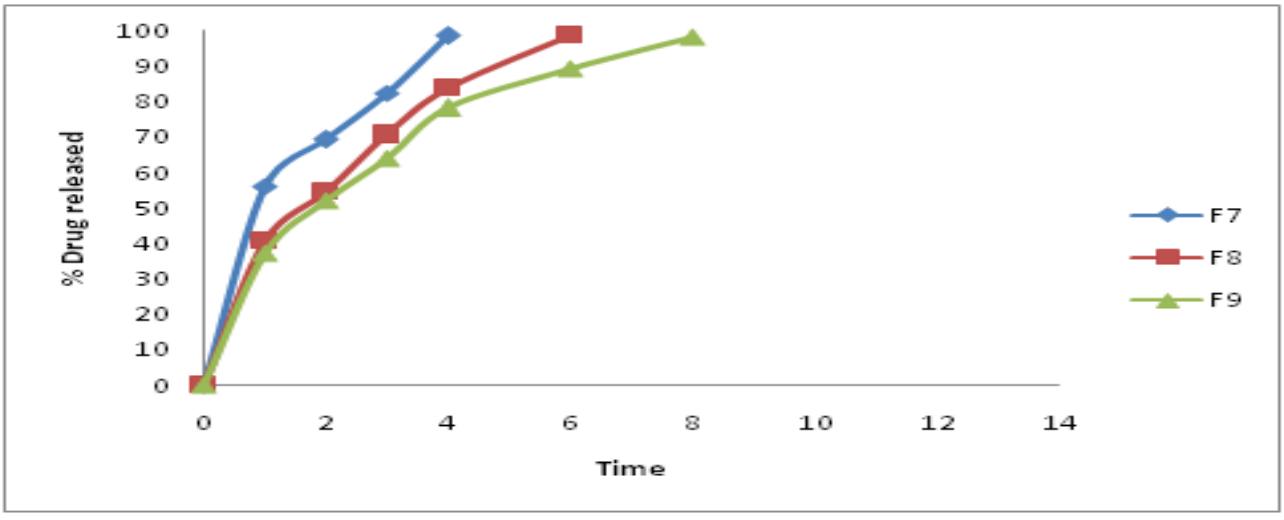

Fig-6 Drug Release Profiles of Metformin HCl Matrix Tablets

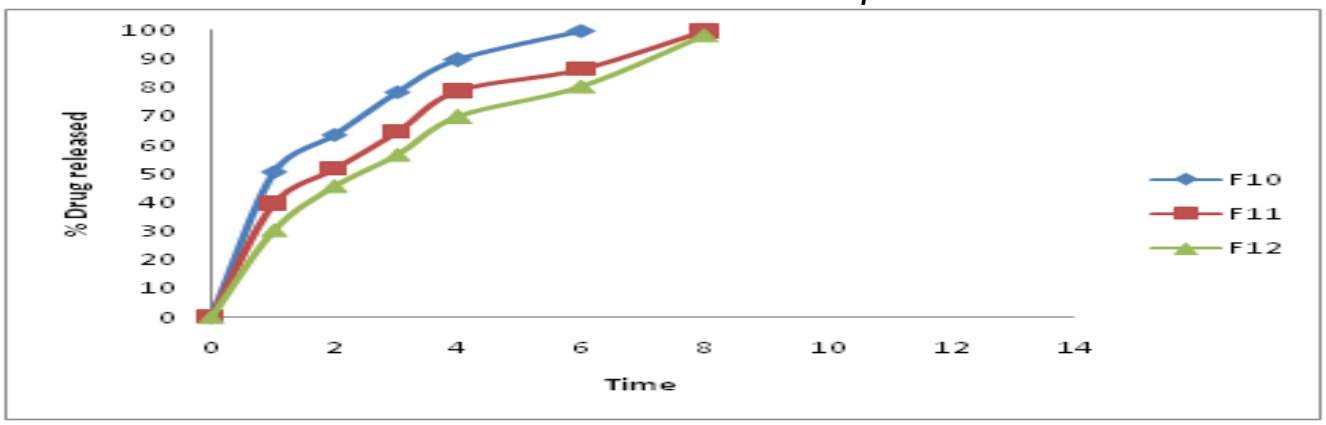

Fig-7 Drug Release Profiles of Metformin HCl Matrix Tablets

Differential Scanning Calorimetry

DSC studies of Metformin HCl and optimized formulations were carried out to study the interaction between the drug and polymers used and the results of the study were shown in Figure 8-10. The DSC thermograms of Metformin showed sharp endothermic peak at 247.80C, while that of Guar gum showed broad endothermic peak at 97.9C. The DSC Thermograms of optimized formulations F5 showed sharp endothermic peaks for Metformin at the temperatures 254.40C. This indicated that there were no drug polymer interactions in the formulations.

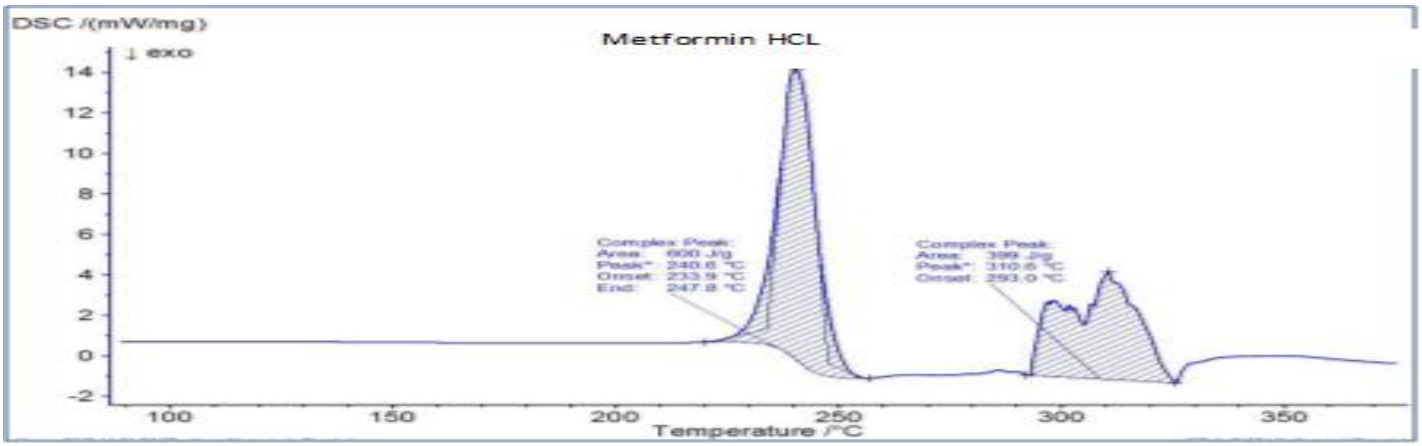

Fig-8 DSC of Pure Drug

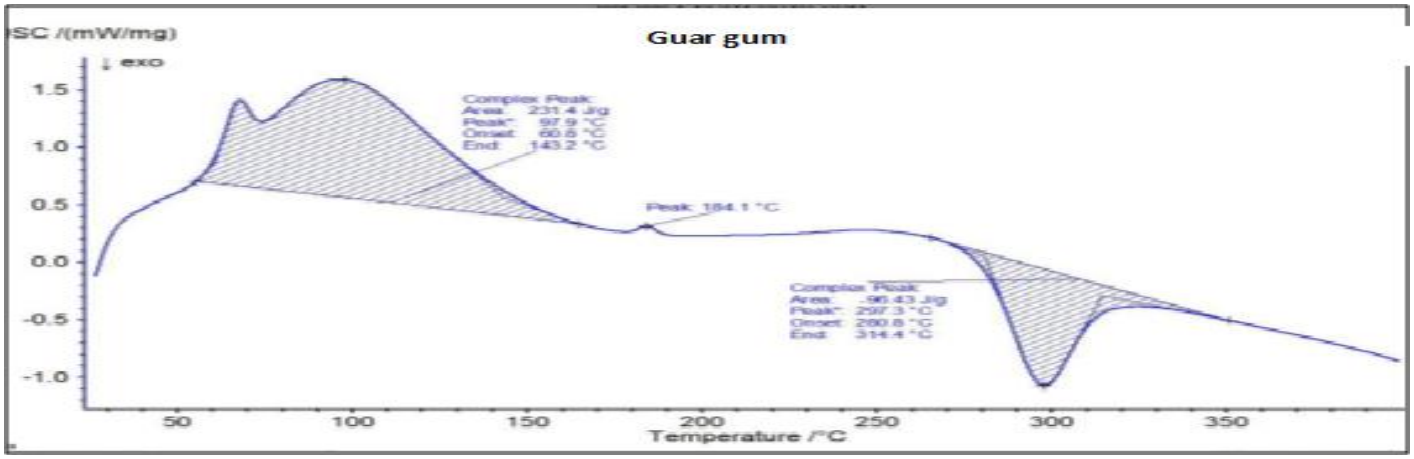

Fig-9 DSC of Guar gum

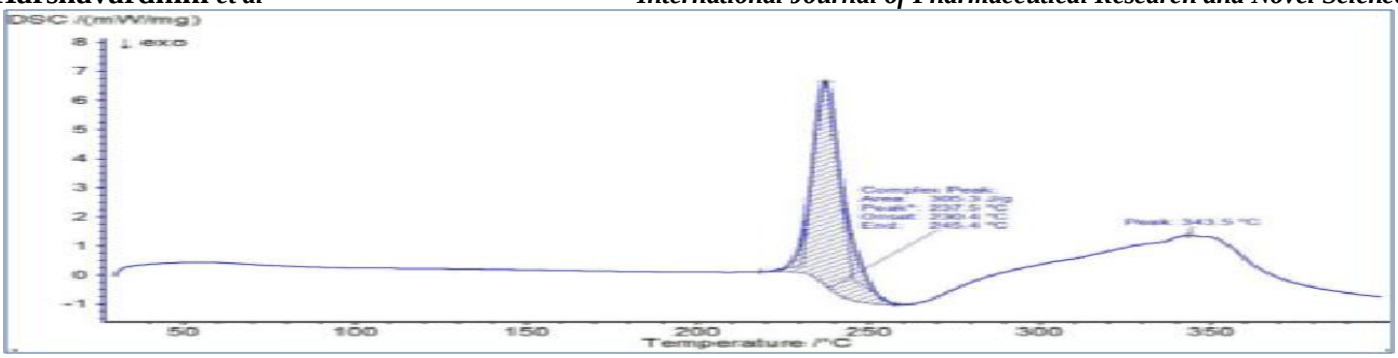

Fig-10 DSC of Drug + Guar gum

CONCLUSION

Metformin HCl is a water soluble drug, sustained release matrix tablets of Metformin HCl were prepared by direct compression method with HPMC K100M, Guar gum, Xanthan gum and Eudragit Rl100 as a rate retarding polymer along with pharmaceutically acceptable excipients. Preformulation studies were performed on the drug and polymers used in the formulations and were found to be compatable. No drug and polymer reactions were observed. The calibration curve for the estimation of Metformin HCl in 0.1NHcl and 6.8 pH phosphate buffer were found to be linear and obeyed Beer's law in the concentration range of 2-10 µg/ml. Flow properties such as Angle of repose and Carr's index were evaluated for the prepared granules and were found to exhibit good flow properties. The angle of repose values obtained for powder mixture were in the range of 25.55-29.51^0 and the Carr's index values were in the range of 18.28 – 20.67%. The zero order R2 values of tablet formulations were in the range of 0.824 to 0.921 Thus all the formulations were found to be non linear with zero order rate constant. The first order R2 values of tablet formulations were in the range of 0.971 to 0.995. Thus all the formulations were found to be linear with first order rate constant. The drug release from the tablets depends on the different polymers employed. Good linear relationships were observed between drug release and different polymers. Polymers such as Guar gum have high influence on extending the drug release over a prolonged period of time. Amount of drug released Vs square root of time plots for all the matrix tablet formulations were found to be linear with R2 values in the range of 0.974 to 0.993. The release exponent 'n' values for all the matrix tablet formulations were in the range of 0.312 to 0.498 indicating that the drug release is by non fickian diffusion. Thus, the drug release from the matrix tablet formulations was by diffusion of the drug from the polymer matrix followed by erosion of the polymer. FTIR and DSC were performed for pure drug, polymer, F5 formulation. The results revealed that there were no major interaction between the drug and polymer.

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